Modifiable risk factors and the development of psoriatic arthritis in people with psoriasis

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ABSTRACT

Objectives To investigate associations between obesity, changes in body mass index (BMI), alcohol intake and smoking status and the development of Psoriatic Arthritis (PsA) in people with psoriasis.

Methods We have undertaken a cohort study involving incident psoriasis cases identified from the UK Clinical Practice Research Datalink between 1998 and 2014. The associations between smoking, alcohol and BMI and development of PsA were assessed using generalised additive models. Additionally, the risks associated with a change in BMI during follow-up were investigated using distributed lag non-linear models.

Results We identified 90,189 incident cases of psoriasis (42% males, mean age 51) of whom 1,409 had a subsequent record of PsA diagnosis. BMIs of 25.0-29.9, 30.0-34.9 and ≥35.0 were significantly associated with an increased risk of developing PsA compared to BMIs of <25.0: OR_{adj} 1.79 (CI_{95} 1.46 - 2.19), OR_{adj} 2.10 (CI_{95} 1.67 - 2.63), and OR_{adj} 2.68 (CI_{95} 2.09 - 3.43), respectively. Reducing BMI over a 10-year period (linearly) was associated with a reduction in the risk of developing PsA when compared to BMI remaining constant over the same period. Increased risks of developing PsA were associated with moderate drinking but not with ex- or heavy drinking or with current or past smoker status.

Conclusion In this incident psoriasis cohort, increased BMI and moderate drinking but not heavy drinking or smoking status were associated with an increased risk of PsA in people with psoriasis. Importantly, we have shown that reducing weight may result in a reduction in the risk of developing PsA.

INTRODUCTION

Psoriatic Arthritis (PsA) is a progressive and often destructive joint disease affecting approximately 20% of people with psoriasis.[1] PsA causes pain, swelling and joint stiffness and is accompanied by chronic disfiguring skin disease and can lead to an impaired quality of life.[2] For the majority of people with psoriasis, PsA is diagnosed after, or synchronously with, the onset of psoriasis,[3] identifying them as a target group for investigating modifiable risk factors in the development of PsA.

While the association between obesity and an increased risk of psoriasis is well documented,[4] fewer studies have investigated its association with the risk of developing PsA. Three studies have found an increased risk of PsA among obese people with psoriasis, with the risk increasing with increasing body mass index (BMI).[5-7] However, these studies have only considered the effect of obesity as a single exposure whereas the effect of obesity on the risk of developing PsA in people with psoriasis may occur with some delay and may change over time.

The role of smoking in the development of PsA is less clear with studies reporting conflicting results.[8-11] The conflicting results may relate to different study designs and timing of smoking measurement. While there is substantial evidence suggesting that alcohol intake is associated with risk of psoriasis, the relationship between alcohol intake and risk of PsA is less established.[12-17] Two studies have found an increase in alcohol consumption to be associated with an increase in the risk of developing PsA.[14, 15] Additional studies are therefore needed to better determine the role of smoking and alcohol in the development of PsA.

The aim of this study was to examine the associations between obesity, changes in BMI, alcohol consumption, smoking status and the development of PsA in people with psoriasis, using data from the Clinical Practice Research Datalink (CPRD). Understanding these modifiable risk factors is essential in determining those who are at the greatest risk of developing PsA, and hence will inform clinical recommendations on potential life-style adjustments that may reduce that risk.

METHODS

Data source

The Clinical Practice Research Datalink (CPRD) contains routinely collected anonymised longitudinal medical records from UK primary care. It is actively collecting data on ~7% of the UK population.[18] It is generally representative of the UK population and has previously been used to study both psoriasis and PsA.[3, 19, 20]

Study design

A cohort study was performed of incident psoriasis cases identified from the CPRD, between 1 January 1998 and 31 December 2014, and followed prospectively until the earliest of (a) the individual developing the outcome of interest PsA; (b) the individual or their practice ceasing to contribute data to the CPRD or (c) the end of the study period.

Study population

The base population consisted of all incident cases of psoriasis, aged 16 to 89 years at the time of diagnosis, who were permanently registered and contributing to the CPRD at any time during the study period, with at least one year of valid data collection.[18]

Identification of cases of psoriasis and PsA

Incident cases of psoriasis diagnosed between 1998 and 2014 were identified, based on Read codes used and validated by previous studies in a similar UK database, which have been demonstrated to have a positive predictive value of 90%.[21, 22] In addition, psoriasis-specific treatment information was used as an indication of a psoriasis diagnosis (see online supplementary text). Cases were classified as incident if they had a minimum of one year of valid data collection before the date of diagnosis.[23]

We searched the psoriasis cohort for incident cases of PsA diagnosed during the study period and after their date of psoriasis diagnosis using Read codes used and validated by a previous study, in a similar UK database, with a positive predictive value of 85%.[21] The date of diagnosis was the date of the first PsA code or date of first disease-modifying anti-rheumatic drug (DMARD) prescription in the absence of evidence of an alternative indication for the DMARD (which included psoriasis, determined based on methotrexate being prescribed on the same date as a psoriasis or dermatology code), whichever was earlier.

Determining smoking, alcohol and BMI status

Smoking and alcohol consumption status were determined using algorithms developed at the University of Bath (see online supplementary text). Smoking status was determined using all available medcodes related to smoking and was classified as smoker, ex-smoker or non-smoker. Alcohol consumption status was determined using all available medcodes related to alcohol/drinking and categorised as heavy drinker (>3.0 units/day), moderate drinker (0.1 – 3.0 units/day), ex-drinker or non-drinker. Baseline smoking and alcohol consumption status was determined based on the associated status covering the psoriasis index date.

All Read codes relevant to BMI or weight that could indicate a BMI and/or weight category were identified. BMI was classified based on the World Health Organisation BMI categories: <25.0, 25.0-29.9, 30.0-34.9, ≥35.0. We did not use a separate category for underweight (<18.5) because <1% of the study population were within this category. Baseline BMI measurements were estimated using a patient's most recent BMI value in the three years before their psoriasis index date. For the secondary analysis the study population was restricted to those who had been registered on the CPRD for a minimum of ten years with at least two distinct BMI measurements, including one within 6 months of the study end (providing it did not occur before their psoriasis index date) and one from a maximum of ten years prior to their study end date. All available BMI values between these two BMI records were used.

Potential confounding variables

Data on potential confounding variables including demographics, severity of psoriasis, diabetes and history of trauma were extracted from the CPRD. In patients who developed PsA during the follow-up period, psoriasis severity was classified using data before the date of PsA diagnosis. Psoriasis was classified as severe if patients had prescriptions for medicines consistent with the treatment of severe disease (e.g. phototherapy, PUVA, or systemic therapies) or evidence of a referral to a dermatologist and as mild in the absence of evidence of severe disease. History of trauma was restricted to trauma of the bone/joint before the index date. Psoriasis duration was determined as the period between psoriasis diagnosis and the earliest of (a) the individual developing PsA; (b) the individual or their practice ceasing to contribute data to the CPRD or (c) the end of the study period. Demographic variables were extracted at baseline.

Statistical Analysis

Descriptive statistics were used to compare baseline demographics while modifiable life style factors associated with the development of PsA were investigated using logistic regression. The final models were adjusted for all significant covariates ($p < 0.05$), which was based on their contribution to the model as defined by their contribution to the likelihood. Chi-squared tests for trend in proportions were used to test linear trends across BMI categories and generalised additive models were used to investigate non-linear associations. Due to the extent of missing data on BMI in the study population we conducted sensitivity analyses to the proximity of BMI measurements to baseline by using 1) nearest available BMI measurement in the three years leading up to psoriasis diagnosis 2) nearest available BMI measurement in the five years leading up to psoriasis diagnosis and 3) nearest available BMI measurement, irrespective of date of occurrence. Non-linear and cumulative effects of BMI were investigated using distributed lag non-linear models. All statistical analyses were conducted with R statistical software, version 3.3.0.

RESULTS

In total 91,169 incident cases of psoriasis were identified. Cases with a prior diagnosis of PsA (n = 863) or the same date of PsA diagnosis (n = 116) were excluded. From the base population of 90,189 incident cases of psoriasis, 1,409 developed PsA after their diagnosis of psoriasis. The overall incidence of PsA within this population was 2.72 per 1000 person-years (CI_{95} 2.57-2.86). Table 1 shows the incidence rates stratified by age and sex with a higher incidence being observed in males.

There were fewer men than women included in the primary analysis population (48%), which was most notable in the highest and lowest BMI categories (Table 2). Lower BMI categories were younger, less likely to have a history of trauma and had a longer psoriasis duration than the higher BMI categories. Other variables were similarly distributed across BMI categories. At baseline, compared to the psoriasis-only group, those who developed PsA were younger (47 vs 51 years), were more likely have severe psoriasis (29% vs 12% severe) and had a shorter mean duration of psoriasis (3.55 vs 5.75 years) (Table 3).

Influence of modifiable life style factors

Compared to those with BMIs of <25.0, there was a significantly increased odds of developing PsA in those with BMIs of 25.0-29.9, 30.0-34.9 and ≥35.0: OR 1.79 (CI_{95} 1.46 - 2.19), OR 2.10 (CI_{95} 1.67 - 2.63), and OR 2.68 (CI_{95} 2.09 - 3.43), respectively, (p for trend <0.0001). Adjustment for potential confounders marginally attenuated the association with results remaining significant (Table 3). Sensitivity analyses to the proximity of BMI measurements to baseline produced identical patterns; an increasing odds of developing PsA with increasing BMI.

No significant associations between past or current smoker compared to non-smoker were found: OR_{adj} 0.83 (CI_{95} 0.69 – 1.02) and OR_{adj} 0.94 (CI_{95} 0.76 – 1.16), respectively. When modelled along with BMI as an interaction term, the direction of the ORs (and the associated risk of developing PsA) for past or current smoker flipped from being negative (protective effect) to positive (increased odds), although remained non-significant (OR_{adj} 1.03 (CI_{95} 0.65 – 1.60) and 1.12 (CI_{95} 0.76 – 1.69), respectively).

There was a significantly increased odds of developing PsA in moderate drinkers, but not in ex- or heavy drinkers, compared to non-drinkers: OR_{adj} 1.57 (CI95 1.16 – 2.11), OR_{adj} 1.06 (CI95 0.69 – 1.62) and OR_{adj} 0.94 (CI95 0.56 – 1.58), respectively.

There were 15,627 (15, 410 psoriasis-only and 217 PsA) subjects who fulfilled the study criteria for the analysis of non-linear and cumulative effects of BMI. Over a ten year period, linear reductions in BMI were associated with a reduction in risk of developing PsA when compared to a constant BMI of the same starting value (Figure 1). Further information can be found in the supplementary material.

DISCUSSION

The overall incidence of PsA in our psoriasis population of 2.72 per 1000 years is similar to findings from a similar primary health record based study.[6] In a prospective study from Toronto the incidence rate was 10 times higher, possibly explained as all patients in the Toronto cohort underwent an annual review by a rheumatologist.[24] The Toronto cohort also recruited over 65% of patients from phototherapy centres, likely capturing those with more severe psoriasis which has been found to be associated with an increased risk of PsA.[24, 25] Nevertheless, the difference could suggest an under-ascertainment of PsA within the CPRD, providing support for studies reporting a high burden of undiagnosed PsA within patients with psoriasis.[26]

Risk factors for the development of PsA for which there is good evidence include nail psoriasis, psoriasis severity and obesity as well as genetic factors such as HLA-B27.[1, 27] Of these factors the only modifiable lifestyle factor is obesity. Here we have shown for the first time that losing

weight over time, could reduce the risk of developing PsA in a population with documented psoriasis. This change in risk can be demonstrated with the use of a BMI risk calculator.

Although studies investigating the association between changes in BMI and the development of PsA among people with psoriasis are limited in number, all have found an association between increased BMI and increased risk of PsA. One study found that BMI in early adulthood increased the risk of PsA, but did not find an association between current BMI and PsA.[5] Two studies found an increased risk of PsA correlated to BMI with associations existing in a dose-dependent fashion.[6, 7] Two studies have investigated the effect of obesity at multiple time points.[6, 7] The first of these investigated the effect of BMI over the 10 years following psoriasis diagnosis and found that those in higher BMI categories had a higher risk of developing PsA.[6] The second study found a graded positive association between gains in weight and the risk in developing PsA.[7] Since the effect of obesity on the risk of developing PsA may in fact occur with some delay and change over time, our analysis took into account both updated BMI measurements over time and the possible non-linear and cumulative effects of BMI, which has not previously been investigated.

There are mechanisms to explain how obesity may be a contributory causative factor for PsA. For instance adipose tissue is a source of inflammatory mediators such as adipokines and proinflammatory cytokines including TNF-α and IL-6 that together with other genetic, environmental and immunological factors may trigger the development of PsA in susceptible individuals with psoriasis.[28] Microtrauma at entheseal sites is postulated as being an important initiating pathogenic event for the development of PsA, and may be enhanced with increasing body weight.[29] Unloading mechanical stress on hind limbs prevents the onset of enthesitis in a

susceptible mouse model.[30] Furthermore, radiological evidence of enthesitis was reported as more frequent in overweight patients with PsA, and even more so in obese patients than in those with normal BMI.[31]

We have confirmed findings from previous studies that moderate alcohol intake was associated with an increased the risk of developing PsA in people with psoriasis, although the association did not hold true for the subgroups of ex-drinkers or heavy drinkers. We also found that severity of psoriasis was associated with an increase in the risk of developing PsA consistent with most previous studies. These findings were based on data extracted at psoriasis onset and unlike BMI status we were not able to assess over time. A limiting factor in our study is the lack of data on secondary care prescribing in the CPRD such as the use of biological agents that may act as confounders or have an interaction with both alcohol intake and psoriasis severity.

Findings of the association between smoking and risk of PsA among people with psoriasis are inconsistent. For example, Tey et al.[15] found no association between smoking and PsA, two studies suggest that smoking protects against PsA,[10, 11] while Li et al.[9] found that smoking had an increased risk of PsA. A recent study by Nguyen et al.[32] explored this 'smoking paradox' and concluded that traditional study design and analytical methods could result in a risk factor paradox in the context of smoking and risk of PsA among patients with psoriasis. While we found no association between smoking status and the development of PsA in people with psoriasis, further analysis revealed that the effect of smoking on the risk of PsA was possibly mediated through the effect of BMI on PsA, i.e. the protective effect of smoking may be associated with lower BMI amongst smokers.

Strengths of our study include its population-based nature, the large number of psoriasis patients and the previous validation of the codes used to identify psoriasis and PsA. The inclusion of only incident psoriasis patients was an advantage when looking at the temporal relationship of BMI and the risk of PsA. A shortcoming is that lifestyle data tends to be opportunistically recorded in the CPRD and those with non-missing lifestyle data may be unrepresentative of the general population and restriction to those with complete data may result in biased analyses.[33, 34] In addition, psoriasis severity was determined based on referrals to a dermatologist or on prescriptions for medicines consistent with the treatment of severe disease. It is possible that psoriasis severity could be associated with treating PsA when the code for PsA has not been entered. Moreover, by using Read codes validated in a similar database we hope to have limited bias due to case ascertainment.[21]

In conclusion, the findings of this study add to the growing evidence that increased BMI is associated with an increased risk of PsA. Furthermore a reduction in BMI over time, albeit not necessarily intentional, was associated with a reduction in the risk of PsA. While more studies are needed to investigate intentional weight loss on the risk of developing PsA, weight reduction amongst obese people with psoriasis may have the potential ability to prevent their excess risk of PsA while providing additional health benefits, including reduced cardiovascular and mortality risks.[35]

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: All authors report grants from the National Institute for Health Research (RP-PG-1212-20007) during the conduct of the study.

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Ethical approval: Ethical approval has been obtained by the CPRD data provider from a Multi-centre Research Ethics Committee (MREC) for all observational studies and the study protocol was approved by the CPRD Independent Scientific Advisory Committee (15_154R).

Transparency declaration

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

References

1. Ogdie A, Weiss P. The Epidemiology of Psoriatic Arthritis. Rheum Dis Clin North Am. 2015 Nov; 41(4):545-568.
2. Rosen CF, Mussani F, Chandran V, et al. Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone. Rheumatology (Oxford). 2012 Mar; 51(3):571-576.
3. Charlton RA, Tillett W, Nightingale AL, et al. Interval between Onset of Psoriasis and Psoriatic Arthritis: Comparing the United Kingdom Clinical Practice Research Datalink with a Hospital-Based Cohort. Rheumatology. 2017 Apr; 56:66-66.
4. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. Nutr Diabetes. 2012 Dec 03; 2:e54.
5. Soltani-Arabshahi R, Wong B, Feng BJ, et al. Obesity in early adulthood as a risk factor for psoriatic arthritis. Arch Dermatol. 2010 Jul; 146(7):721-726.
6. Love TJ, Zhu Y, Zhang Y, et al. Obesity and the risk of psoriatic arthritis: a population-based study. Annals of the rheumatic diseases. 2012 Aug; 71(8):1273-1277.
7. Li W, Han J, Qureshi AA. Obesity and risk of incident psoriatic arthritis in US women. Ann Rheum Dis. 2012 Aug; 71(8):1267-1272.
8. Rakkhit T WB, Nelson TS, Hansen CB, Papenfuss JS, Panko J, et al. Time to development of psoriatic arthritis decreases with smoking prior to psoriasis onset and increases with smoking after psoriasis onset. J Invest Dermatol. 2007:127.
9. Li W, Han J, Qureshi AA. Smoking and risk of incident psoriatic arthritis in US women. Ann Rheum Dis. 2012 Jun; 71(6):804-808.
10. Eder L, Law T, Chandran V, et al. Association between environmental factors and onset of psoriatic arthritis in patients with psoriasis. Arthritis Care Res (Hoboken). 2011 Aug; 63(8):1091-1097.
11. Pattison E, Harrison BJ, Griffiths CE, et al. Environmental risk factors for the development of psoriatic arthritis: results from a case-control study. Ann Rheum Dis. 2008 May; 67(5):672-676.
12. Brenaut E, Horreau C, Pouplard C, et al. Alcohol consumption and psoriasis: a systematic literature review. J Eur Acad Dermatol Venereol. 2013 Aug; 27 Suppl 3:30-35.
13. Kirby B, Richards HL, Mason DL, et al. Alcohol consumption and psychological distress in patients with psoriasis. Br J Dermatol. 2008 Jan; 158(1):138-140.
14. Wu S, Cho E, Li WQ, et al. Alcohol intake and risk of incident psoriatic arthritis in women. J Rheumatol. 2015 May; 42(5):835-840.
15. Tey HL, Ee HL, Tan AS, et al. Risk factors associated with having psoriatic arthritis in patients with cutaneous psoriasis. J Dermatol. 2010 May; 37(5):426-430.
16. Farkas A, Kemeny L. Alcohol, liver, systemic inflammation and skin: a focus on patients with psoriasis. Skin Pharmacol Physiol. 2013; 26(3):119-126.

17. Qureshi AA, Dominguez PL, Choi HK, et al. Alcohol intake and risk of incident psoriasis in US women: a prospective study. Arch Dermatol. 2010 Dec; 146(12):1364-1369.
18. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015 Jun; 44(3):827-836.
19. Edson-Heredia E, Zhu B, Lefevre C, et al. Prevalence and incidence rates of cardiovascular, autoimmune, and other diseases in patients with psoriatic or psoriatic arthritis: a retrospective study using Clinical Practice Research Datalink. J Eur Acad Dermatol Venereol. 2015 May; 29(5):955-963.
20. Charlton R, Green A, Shaddick G, et al. Risk of uveitis and inflammatory bowel disease in people with psoriatic arthritis: a population-based cohort study. Ann Rheum Dis. 2018 Feb; 77(2):277-280.
21. Ogdie A, Alehashemi S, Love TJ, et al. Validity of psoriatic arthritis and capture of disease modifying antirheumatic drugs in the health improvement network. Pharmacoepidemiol Drug Saf. 2014 Sep; 23(9):918-922.
22. Seminara NM, Abuabara K, Shin DB, et al. Validity of The Health Improvement Network (THIN) for the study of psoriasis. The British journal of dermatology. 2011 Mar; 164(3):602-609.
23. Lewis JD, Bilker WB, Weinstein RB, et al. The relationship between time since registration and measured incidence rates in the General Practice Research Database. Pharmacoepidemiol Drug Saf. 2005 Jul; 14(7):443-451.
24. Eder L, Haddad A, Rosen CF, et al. The Incidence and Risk Factors for Psoriatic Arthritis in Patients With Psoriasis: A Prospective Cohort Study. Arthritis Rheumatol. 2016 Apr; 68(4):915-923.
25. Ogdie A, Langan S, Love T, et al. Prevalence and treatment patterns of psoriatic arthritis in the UK. Rheumatology (Oxford). 2013 Mar; 52(3):568-575.
26. Yang Q, Qu L, Tian H, et al. Prevalence and characteristics of psoriatic arthritis in Chinese patients with psoriasis. J Eur Acad Dermatol Venereol. 2011 Dec; 25(12):1409-1414.
27. Winchester R, Minevich G, Steshenko V, et al. HLA associations reveal genetic heterogeneity in psoriatic arthritis and in the psoriasis phenotype. Arthritis Rheum. 2012 Apr; 64(4):1134-1144.
28. Russolillo A, Iervolino S, Peluso R, et al. Obesity and psoriatic arthritis: from pathogenesis to clinical outcome and management. Rheumatology (Oxford). 2013 Jan; 52(1):62-67.
29. McGonagle D, Lories RJ, Tan AL, et al. The concept of a "synovio-entheseal complex" and its implications for understanding joint inflammation and damage in psoriatic arthritis and beyond. Arthritis Rheum. 2007 Aug; 56(8):2482-2491.
30. Jacques P, Lambrecht S, Verheugen E, et al. Proof of concept: enthesitis and new bone formation in spondyloarthritis are driven by mechanical strain and stromal cells. Ann Rheum Dis. 2014 Feb; 73(2):437-445.
31. Eder L, Abji F, Rosen CF, et al. The Association Between Obesity and Clinical Features of Psoriatic Arthritis: A Case-control Study. J Rheumatol. 2017 Apr; 44(4):437-443.
32. Nguyen UDT, Zhang Y, Lu N, et al. Smoking paradox in the development of psoriatic arthritis among patients with psoriasis: a population-based study. Ann Rheum Dis. 2018 Jan; 77(1):119-123.
33. Booth HP, Prevost AT, Gulliford MC. Severity of obesity and management of hypertension, hypercholesterolaemia and smoking in primary care: population-based cohort study. J Hum Hypertens. 2016 Jan; 30(1):40-45.

34. Bhaskaran K, Forbes HJ, Douglas I, et al. Representativeness and optimal use of body mass index (BMI) in the UK Clinical Practice Research Datalink (CPRD). BMJ Open. 2013 Sep 13; 3(9):e003389.
35. Peltonen M. Obesity, surgically induced weight loss, and cardiovascular disease. Trends Cardiovasc Med. 2016 Apr; 26(3):290-291.

Tables and Figures

Table 1 Incidence Age and sex specific incidence of PsA within the incident psoriasis cohort in the CPRD, per 10 000 person-years.

	Males				Females				All			
Age at psoriasis diagnosis	**PsA cases**	**PYs**	**IR**	**95% CI**	**PsA cases**	**PYs**	**IR**	**95% CI**	**PsA cases**	**PYs**	**IR**	**95% CI**
18-29	72	29421	2.45	1.88 - 3.01	66	32252	2.05	1.55 - 2.54	138	61673	2.24	1.86 - 2.61
30-39	151	36628	4.12	3.47 - 4.78	105	39135	2.68	2.17 - 3.2	256	75763	3.38	2.97 - 3.79
40-49	213	47763	4.46	3.86 - 5.06	148	45772	3.23	2.71 - 3.75	361	93535	3.86	3.46 - 4.26
50-59	171	47786	3.58	3.04 - 4.11	176	47007	3.74	3.19 - 4.3	347	94793	3.66	3.28 - 4.05
60-69	103	46661	2.21	1.78 - 2.63	127	48433	2.62	2.17 - 3.08	230	95094	2.42	2.11 - 2.73
70-79	28	31270	0.9	0.56 - 1.23	31	35853	0.86	0.56 - 1.17	59	67123	0.88	0.65 - 1.1
80-89	7	12046	0.58	0.15 - 1.01	9	18635	0.48	0.17 - 0.8	16	30681	0.52	0.27 - 0.78
All	**745**	**251574**	**2.96**	**2.75 - 3.17**	**664**	**267087**	**2.49**	**2.3 - 2.68**	**1409**	**518661**	**2.72**	**2.57 - 2.86**

Table 2 Baseline characteristics of study participants. All variables were based on those measured at the time of psoriasis diagnosis, except for BMI which was based on nearest available BMI measurement in the three years leading up to psoriasis diagnosis.

	All (n=90189)	**Psoriasis only** (n=88780)	**PsA** (n=1409)
Sex (%)			
Female (Reference)	46590 (52)	45926 (52)	664 (47)
Male	43599 (48)	42854 (48)	745 (53)
Age, mean (SD), years	48.34 (18.22)	48.51 (18.29)	44.70 (13.88)
Psoriasis duration, mean (SD), years	5.71 (4.10)	5.75 (4.11)	3.55 (3.36)
History of Trauma, (n, %)	17206 (19)	16941 (19)	265 (19)
Diabetes, (n, %)			
None (Reference)	81201 (90)	79953 (90)	1248 (89)
Type I	251 (0)	250 (0)	1 (0)
Type II	8737 (10)	8577 (10)	160 (11)
Psoriasis severity, (n, %)			
Mild (Reference)	78698 (87)	77697 (88)	1001 (13)
Severe	11491 (13)	11083 (71)	408 (29)
BMI category, (n, %)			
<25 (Reference)	15519 (17)	15384 (17)	135 (10)
25.0-29.9	15841 (18)	15603 (18)	238 (17)
30.0-34.9	8980 (10)	8818 (10)	162 (11)
35>=	5854 (6)	5728 (6)	126 (9)
Missing	43995 (49)	43247 (49)	748 (53)
Smoking status, (n, %)			
Non-smoker (Reference)	38452 (43)	37808 (42)	644 (46)
Ex-smoker	25039 (28)	24646 (28)	393 (28)
Current smoker	25133 (28)	24768 (28)	365 (26)
Missing	1564 (2)	1558 (2)	7 (0)
Alcohol status, (n, %)			
Non-drinker (Reference)	9883 (11)	9745 (11)	138 (10)
Moderate drinker	60002 (67)	58982 (66)	1020 (72)
Heavy drinker	3995 (4)	4370 (5)	60 (4)
Ex-drinker	4430 (5)	3942 (5)	53 (4)
Missing	11879 (13)	11741 (13)	138 (10)

Table 3 Associations between modifiable life style factors and PsA.

	Unadjusted			Adjusted[†]		
	OR	CI_{95}	*P*	OR	CI_{95}	*P*
BMI category[a]						
<25 (Reference)	1.00	-	-	1.00	-	-
25.0-29.9	1.79	1.46 - 2.19	<0.0001	1.76	1.41 - 2.19	<0.0001
30.0-34.9	2.10	1.67 - 2.63	<0.0001	2.04	1.60 - 2.60	<0.0001
35>=	2.68	2.09 - 3.43	<0.0001	2.42	1.85 – 3.16	<0.0001
Smoking status[b]						
Non-smoker (Reference)	1.00	-	-	1.00	-	-
Ex-smoker	0.92	0.77 – 1.10	0.3650	0.83	0.69 - 1.02	0.0733
Current smoker	0.95	0.78 – 1.15	0.5850	0.94	0.76 - 1.16	0.5442
Alcohol status[c]						
Non-drinker (Reference)	1.00	-	-	1.00	-	-
Moderate drinker	1.53	1.40 – 2.06	0.004	1.57	1.16 – 2.11	0.0033
Heavy drinker	1.20	0.72 – 2.00	0.4713	0.94	0.56 - 1.58	0.8216
Ex-drinker	1.25	0.82 – 1.90	0.2982	1.06	0.69 - 1.62	0.7848

[†]The following covariates were considered for adjustment in the model; sex, age, psoriasis duration, history of trauma, diabetes, psoriasis severity and, where appropriate, BMI, smoking and alcohol. The final models were adjusted for all significant covariates ($p < 0.05$); [a]Adjusted for age, psoriasis duration, psoriasis severity and alcohol status [b]Adjusted for age, psoriasis duration, psoriasis severity and BMI category [c]Adjusted for age, psoriasis duration, psoriasis severity, alcohol status and BMI category. Results were robust to sensitivity analysis in which psoriasis severity was restricted to evidence of a prescription for a treatment consistent with severe disease only and did not include dermatology referrals.

Figure 1 Risk calculator for BMI and developing PsA. Here risk, measured as an odds ratio, was estimated using a Distributed lag non-linear model, which represents a modelling framework to flexibly describe associations showing potentially non-linear and delayed effects. This figure shows the differences between the cumulative risk associated with a linear change in BMI over a 10 year period and that with remaining at a constant BMI (with each case starting from the same value). The change in risk is the difference between the risks at ten years from the two cases, expressed as a percentage (of BMI remaining constant). Positive changes (shown in red) indicate an increase in risk with negative changes (in green) indicating reduced risk. For example, consider an individual with a BMI of 30 and two different scenarios: (i) they reduce their BMI from 30 to 25; (ii) they remain at a constant BMI of 30. Compared to remaining at a constant BMI of 30, reducing BMI from 30 to 25 reduces the cumulative risk of developing PsA by 13%.

KEY MESSAGES

What's already known about this topic?

- There is some evidence that increased BMI is associated with an increased risk of developing PsA and conflicting results surrounding the relationship between smoking and the development of PsA among patients with psoriasis.

What does this study add?

- Using non-linear and lagged effect of BMI measured over time we have shown that reducing BMI may be associated with a reduction in the risk of developing PsA
- We have found no evidence that smoking alters the risk of developing PsA in patients with psoriasis